16 REGULATION OF INFLAMMATION BY CELL DEATH IN ALLERGIC RHINITIS

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KEY MESSAGES

- Delayed eosinophil apoptosis contributes to tissue eosinophilia and is driven by IL-5
- Eosinophil activation leads to eosinophil cytolysis, a non-apoptotic type of cell death
- Successful therapies delete eosinophils from tissues
- Specific cell death pathways should be considered as targets for anti-allergic therapies

The regulation of cell death in allergic rhinitis (AR) has been relatively little investigated and its possible contribution to pathogenesis largely ignored. As with other types of inflammatory responses, the local accumulation of different subgroups of leukocytes occurs during the initiation and maintenance phases, whereas inflammatory cell numbers decline in the resolution phase of allergic inflammation. The changes in cell numbers during inflammation are largely due to changes in rates, both of cell recruitment and of cell death. Important leukocyte subgroups believed to play critical roles in the pathophysiology of AR are the dendritic cells, T cells, mast cells, and eosinophils.

The contribution of cell death to the pathogenesis of allergic diseases has recently been summarized elsewhere. Although most of the reports published so far have not been studies with AR patients or animal models, one could expect that these findings should have relevance for AR. For instance, it is likely that epithelial cell damage accompanies the allergic inflammation of the nasal mucosa. Moreover, the susceptibility of T cells for undergoing apoptosis might be regulated similarly to other inflammatory responses.

The mode of cell death in eosinophils has been the subject of most studies on cell death regulation and inflammation in AR. Eosinophils accumulate in the nasal mucosa not only owing to increased recruitment, but also as a consequence of delayed apoptosis. The major eosinophil survival factor seems to be IL-5. Interestingly, allergen-specific immunotherapy reduced IL-5 production by CD4+ T cells in AR patients and anti-IL-5 antibody therapy has been effective in patients with nasal polyposis. The beneficial effect of topical corticosteroid therapy in AR is probably also largely a consequence of the reduced expression of Th2 cytokines, including IL-5. Besides delayed eosinophil apoptosis, eosinophil degranulation and cytolysis, which represents a form of non-apoptotic cell death, have also been observed in AR. It has been suggested that eosinophil cytolysis occurs without prior extensive degranulation and is the result of major activation mechanisms distinct from degranulation. The molecular mechanisms of eosinophil activation resulting in cytolysis remain to be investigated.

A look at the molecular basis of many allergic diseases reveals a cell death component that either accounts for the disease or contributes to disease progression. For instance, following eosinophil activation in AR, signaling pathways mediating both cell survival and cell death are activated. Regardless the cellular response, the inflammation is maintained (Fig. 1). Therefore, current and future

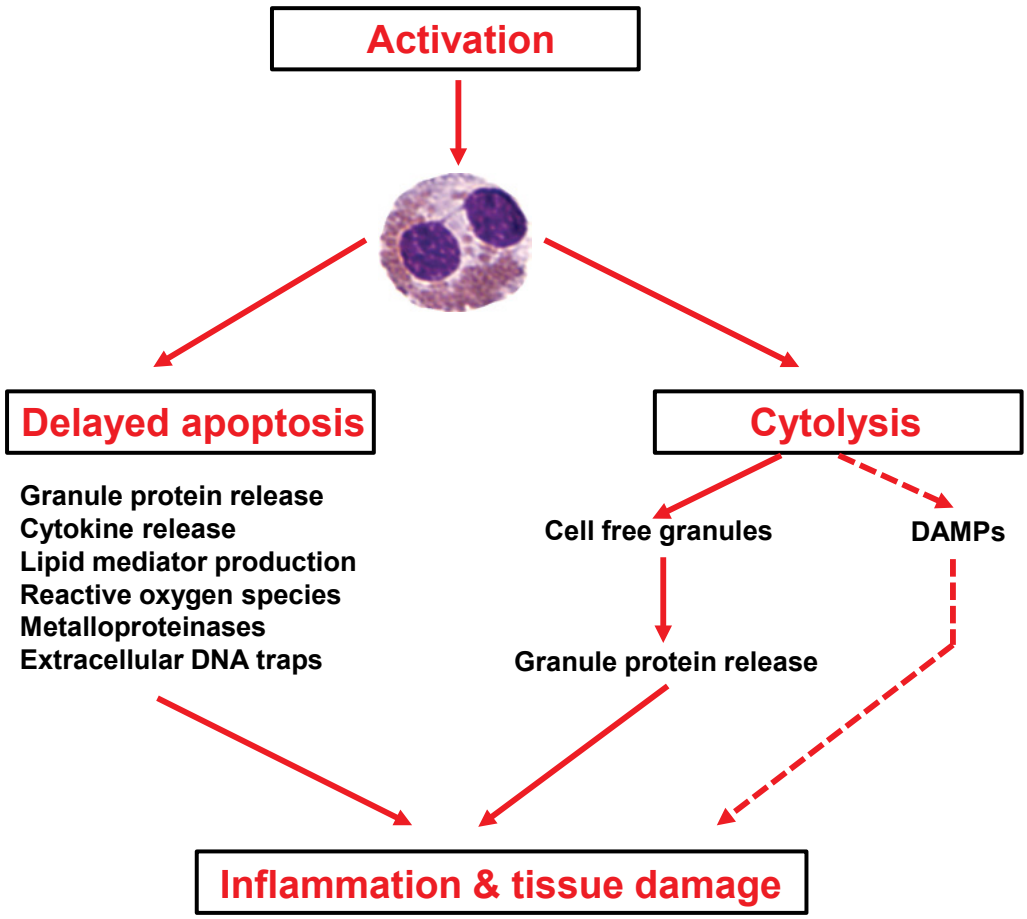

Figure 1 Eosinophil activation and their cellular life span. The activation of eosinophils can change their cellular life span. Either eosinophils exhibit a prolonged life span owing to cytokine-mediated delayed apoptosis or they undergo cytolysis. With delayed apoptosis, eosinophils contribute to the maintenance of inflammation by multiple mechanisms. Cytolysis, on the other hand, is associated with massive granule protein secretion. Moreover, cytolysis most likely results in the release of damage-associated molecular pattern molecules (DAMPs), which are known to trigger inflammatory responses. The release of DAMPs from cytolytic eosinophils remains to be further studied; hence, this pathway is indicated with dashed arrows.

anti-allergic therapies should also be analyzed with respect to their impact on cell death pathways.

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